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AIR-WAY RESISTANCE CHANGES IN MEN EXPOSED TO GB VAPOUR

By

M. AINSWORTH AND J.W. EVELEIGH

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SUMMARY

Changes in lung air-way resistance to flow in men exposed by inhalation to GB vapour have been estimated. Measurable increases resulted from the administration of doses larger than 1.0 microgram per kg.

In nearly every case, the increase was maximal immediately after gassing and then diminished fairly rapidly in an exponential manner. The degree of the effect appeared to depend on the dose and the concentration of the inhaled GB vapour.

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INTRODUCTION

The failure of respiration in poisoning by the nerve gases is a result of interference by these agents with nearly all the mechanisms which normally form a co-ordinated ventilating system. Thus near critical doses may produce inhibition of the respiratory centres, impaired functioning of the respiratory muscles, increased secretions in the air-ways, and narrowing of the air-ways. The last two effects are of considerable importance if they offer an appreciable mechanical obstruction to air-flow in the lungs for, in addition to contributing to early respiratory failure, they may impede efforts to maintain adequate ventilation by artificial means.

Efforts to assess the degree of bronchial obstruction produced in humans by small doses of GB have led to somewhat vague results. Cooper and Maloney (1), estimating the effect by the Maximum Breathing Capacity test, reported a significant fall in MBC with dosages (Ct.) up to 6 mg.min./m^3. Clements and his co-workers (2) however, as a result of measurements using the method of Otis and Proctor (3), concluded that the increase in air-way resistance with these low dosages was insignificant. Further work (4), in which the MBC test was employed, failed to show definite evidence of bronchial obstruction with larger dosages (up to 20 mg.min./m^3), although there was a trend in the data towards a reduction in MBC. More recent work (5) also failed to gain evidence of bronchial obstruction.

The experimental results presented in this paper show that, in humans, the inhalation of more than 1.0 microgram/kg. of GB increases the lung resistance to flow, the effect being of a transient nature, and maximal immediately after absorption of the dose.

METHODS

1. Gassing

The use of Ct. as a measure of the dose was avoided for reasons of precision and safety. Measurements of the GB vapour concentrations and the volumes of air respired allowed more satisfactory estimates to be made of the doses in terms of the mass of GB absorbed. Doses from 0.6 - 3.0 micrograms/kg. were administered. The apparatus

described by Childs et al (6) was employed in most of the experiments. The subject inhaled orally from a two-way valve system, the volume of the expired air being measured with a direct-indicating spirometer. A two-way tap connected the subject either to fresh air or to a 100 m^3 chamber in which the GB concentration was maintained. The retention of GB vapour inhaled orally has been estimated to be approximately 85% (7), and a correction by this factor was made in calculating the dose. In some experiments, the device shown in Fig. 3 was used. To charge the system, the main tube A of about 500 cc. in volume was evacuated to about 0.01 mm. Hg. The required dose of pure GB was dropped into a side vapouriser tube B using a recent development of a microburette previously described (8). The space volume of the vapouriser tube was as small as possible (about 1.0 cc.) and the tube was enclosed by a "basket" heater of nichrome wires capable of dissipating 30 - 40 watts. The tap between tubes A and B was opened and the heater switched on. The internal surface temperature of the vapouriser tube rose to about 60°C. within a few seconds, and the GB had evaporated in this time. Dry air was then admitted by opening tap T_1. The subject, wearing a nose-clip, exhaled fully and then inhaled orally from tube C, taps T2 and T3 having been opened. The inhaled volume was usually more than two litres, and tests with a mechanical system pumping this volume of air through the apparatus gave recoveries of 85 - 100% of the amount of GB evaporated.

2. Lung Resistance

Changes in lung resistance to air-flow were estimated using a resistance-interrupter method (9), and the electronic instrument already described (10). Values of air-way resistance for each individual are expressed in terms of the control value obtained before the experiment.

RESULTS

With few exceptions in more than sixty subjects, the air-way resistance to flow increased appreciably after the inhalation of the GB vapour. Table 1 shows the results of experiments in which, with the exception of the first group, tests were carried out 10 - 15 minutes after gassing. The mean values appear to show some correlation between dose and increase in lung resistance. The smallest doses (first group) in these experiments, however, produced effects which seemed disproportionately large, but, as will be shown, this apparent discrepancy was probably due to the difference in timing of the tests. In most cases, inhibition of the blood Ch E was estimated, the results being included in Table 1.

TABLE 1

THE INCREASE IN LUNG AIR-WAY RESISTANCE FOLLOWING EXPOSURE TO GB VAPOUR

Subject	Conc. (mg./m^3)	Dose (µg./kg.)	Time (min. after gassing)	Blood ChE depression (%)	Lung Resistance (x normal)
All	2.5	0.75	1	0	1.40
Bre		0.84		0	1.48
Pin.		1.08		0	1.56
Cra		0.58		0	1.19
Sco		0.65		7	1.25
Mean		0.78		0	1.37
Chap	4.9	1.17	10	4	1.40
Sh		1.35		7	1.35
McK		1.29		11	1.56
Ca		1.20		16	1.25
Ell		2.70		37	1.75
Mean		1.54		15	1.48
Ae	5.0	1.40	15	10	1.00
Et		1.35		6	1.08
Va		1.45		15	1.00
Mean		1.45		10	1.03
Je	7.5	1.34	10	14	1.26
Fe		2.06		23	1.33
Th		2.06		23	1.30
Car		2.10		17	1.09
San		1.30		12	1.31
Mean		1.77		18	1.26
Ro	10	2.07	10	-	1.40
McD		2.10		-	1.50
Woo		2.10		-	1.50
Wat		2.07		-	2.10
Mean		2.09			1.62
She	10	2.96	10	38	2.12
Bur		2.92		42	1.67
Dil		3.01		32	1.97
Bee		2.60		27	1.58
Kin.		2.87		46	1.50
Mean		2.87		37	1.77

Table 2 shows the results of further experiments in which estimates of air-way resistance were made at various times after gassing.

TABLE 2

The variation of lung air-way resistance with time after inhalation of GB vapour

Subject	Concn. inhaled (µg./m³)	Volume respired (litres)	Dose absorbed (µg./kg.)	Lung Air-way Resistance (x normal)										
				Time after gassing (minutes)										
				1	2	5	7	10	15	30	1 hr.	2 hr.	4 hr.	24 hr.
Coa	5	10	0.83	-	1.65	1.25	-	-	1.10	1.00	-	1.07	-	-
Jon		10	0.67	-	1.40	1.40	-	-	1.06	1.12	-	1.06	-	-
Ls		20	1.50	1.63	-	-	1.22	-	1.00	-	1.00	-	-	-
St.		20	1.30	1.36	-	-	1.08	-	1.08	-	1.02	-	-	-
La		20	1.40	1.18	-	-	0.95	-	1.00	-	1.00	-	-	-
Hah		20	1.47	1.65	-	1.35	-	-	-	1.40	1.15	-	-	1.06
Lo		20	1.60	1.57	-	1.28	-	-	-	1.23	1.20	-	-	1.03
Cur		30	2.30	-	-	-	1.20	-	1.05	0.93	-	1.13	-	1.09
Tar		30	2.10	-	-	1.60	1.23	1.35	1.18	-	1.16	1.20	-	1.12
SHe	10	20	2.96	-	-	-	-	2.12	-	1.80	-	1.20	-	1.20
Bur		20	2.92	-	-	-	-	1.67	-	1.12	-	0.91	-	1.00
Dil		20	3.01	-	-	-	-	1.58	-	1.16	-	1.07	-	-
Bee		20	2.60	-	-	-	-	1.97	-	1.53	-	-	-	1.23
Kin.		20	2.87	-	-	-	-	1.50	-	1.26	-	1.40	-	1.25
Edw	13.7	4	0.78	1.30	-	1.26	-	1.24	-	1.06	1.00	0.89	-	0.95
Trot	13.1	12	2.40	2.10	-	1.56	-	1.40	-	1.12	-	1.34	-	1.06
Smi	15	6.8	1.56	1.75	-	1.42	-	-	1.46	1.29	-	1.02	-	-
Coo	15	7.3	1.70	2.02	-	1.35	-	-	1.23	1.12	-	1.17	-	1.05
Hay	15	7.0	1.66	1.78	-	1.36	-	-	1.28	1.06	-	0.97	-	-
Dic	15	7.2	1.65	2.11	-	1.43	-	-	1.50	1.38	-	1.13	-	1.03

TABLE 2 (contd.)

Subject	Concn. Inhaled (mg./m3)	Volume respired (litres)	Dose absorbed (µg./kg.)	Lung air-way Resistance (x normal) Time after gassing (minutes)										
				1	2	5	7	10	15	30	1 hr.	2 hr.	4 hr.	24 hr.
Hyn	22	8	2.0	2.60	2.10	1.66	1.55	-	1.14	1.27	-	1.56	-	1.30
Lew		8	2.1	1.48	-	1.06	-	1.00	1.17	-	-	1.06	0.95	1.02
Woc		8	1.95	1.75	-	1.60	-	1.40	1.30	1.30	-	1.14	1.14	1.04
Cal		12	2.9	1.90	1.70	1.70	-	-	1.43	-	1.23	-	1.30	1.04
Hina		12	3.1	2.57	1.56	1.60	-	-	1.56	1.50	1.50	-	1.26	1.32
Coop		12	2.7	2.31	1.85	1.83	-	-	1.62	-	1.55	-	1.22	0.95
Ell	30	3.2	1.5	-	4.40	-	-	-	2.82	-	1.61	1.60	-	1.50
Gre		3.4	1.34	-	2.16	-	-	-	2.10	-	1.95	1.64	-	1.30
Prie		3.0	1.27	-	1.84	-	-	-	1.56	-	1.33	1.33	-	1.09
Kah		3.0	1.40	-	2.14	-	-	-	1.59	-	1.19	1.23	-	1.05
Gos	35	3.0	1.49	3.10	-	2.07	-	1.80	-	1.80	2.10	1.40	-	1.10
Fen		2.8	1.41	2.75	-	2.40	-	1.94	-	2.00	1.82	1.35	-	1.17
Wid		3.4	1.74	3.00	-	2.20	-	1.86	-	1.33	1.33	1.25	-	0.89
Sta	40	3.0	1.50	2.20	-	-	-	2.00	-	2.00	1.52	-	1.28	0.96
Ken		3.0	1.35	4.09	-	-	-	1.88	-	1.57	1.18	-	-	1.10
Wil		3.0	1.40	2.62	2.49	-	-	1.75	-	-	1.70	-	1.57	1.23

In nearly every case, the estimated air-way resistance increased to a peak value immediately after gassing. The resistance then diminished fairly rapidly, in some instances approaching the control value within 15 - 30 minutes. The time taken for the resistance value to return to normal depended on the degree of the initial effect. In a few cases an effect was measurable for more than 24 hours.

The subjective symptoms were described in a variety of ways. Most subjects, however, reported a transient "tightness in the throat" together with a more persistent "chestiness" sometimes described as being "a bit harder to breathe". These symptoms occurred during or immediately after inhaling the GB, and it was clear in some cases that the expiratory flow rates attainable were reduced. This was indicated by the lowered pressure differentials in the external resistance to flow. For a minute or so after gassing these subjects, in spite of repeated requests were unable to exhale with flow rates as high as in the control tests.

The data in Table 2 were broadly analysed in two ways. Fig.1 shows the variation of average lung air-way resistance with time after gassing for selected groups in which the individuals received about the same dose. Fig.2 shows a similar plot of data for groups in which the individuals were exposed to the same concentration. Although complicated by the variation in average concentration from group to group, Fig.1 appears to indicate that the effect depended to some extent on the dose. Fig.2 shows that the magnitude of the effect was also dependent on the concentration of the vapour inhaled.

DISCUSSION

The experiments described have shown that an inhaled dose of GB vapour greater than 1.0 microgram/kg. and at a concentration higher than 5 mg./m^3 produces a measurable increase in lung air-way resistance. Such a dose corresponds to a resting exposure to a dosage (Ct.) greater than 10 mg.min./m^3 ($t < 2$ min.). The maximum increase in lung resistance occurred almost immediately after inhalation of the GB. This finding contrasts with that of Cooper and Maloney (1) whose experiments indicated that the maximum degree of air-way obstruction occurred from 15 minutes to 2 hours after gassing.

In a few cases, the lung resistance to flow increased for some minutes to as much as three to four times the normal value without causing any significant respiratory embarrassment. The respiratory reserve is normally large, and Comroe (11) has already pointed out that a substantial resistance to air-flow in the lungs can be tolerated in otherwise normal subjects. With larger doses of GB however, other factors which reduce the available respiratory effort would tend to make an air-way obstruction less tolerable.

The symptom described by the subjects as "chest tightness" or "a bit harder to breathe" seemed to follow the air-way obstruction in degree. Most subjects said that the effect was most noticeable immediately after gassing, and that it had disappeared or was considerably diminished after 15 - 30 minutes. Nevertheless, some subjects subsequently claimed to have experienced occasional "chestiness" over 24 hours,

[illegible] ir-way resistance coefficient had [illegible] al. Repeated tests on a few normal [illegible] sistance to be constant within the [illegible] s of months, and it is possible that a [illegible] nge in lung resistance requiring even a s[illegible] ratory effort.

T[illegible] stance appeared to depend on the dose and on the con[illegible] aled GB vapour. Limited experiments were carried out [illegible] centration range, the apparatus shown in Fig.3 being emp[illegible] .4 micrograms/kg. were administered to five subjects as a sing[illegible] n taking from 5 - 8 seconds. The average value of the peak air-way [illegible] ance expressed in terms of the normal resistance was 2.55 (range 1.98 - [illegible] 90). The increase was therefore slightly smaller than that found with concentrations from 30 - 40 mg./m^3 and similar doses. The concentration of GB in the apparatus was about 200 mg./m^3 but it was undoubtedly much reduced when mixed with the volume of air inhaled (more than 2 litres).

The transient nature of the air-way obstruction seemed to indicate a local effect followed by circulatory clearance of the active agent. Blood clearance of various agents has been shown (12), (13) to be a first order process, and the reduction of air-way resistance after gassing roughly followed such a relation with time. It is therefore of some interest, especially from the aspect of extrapolation from the present results, to consider the situation where the active agent is appearing in tissues at a constant rate and is being removed at a rate proportional to the amount of agent present. Suppose the rate of appearance of the active agent is <u>aCV</u>, where

a = constant,

C = concentration of inhaled vapour,

V = volume of air respired in unit time, and let

k = exponential clearance constant, and

E = amount of agent present in the tissues at the time <u>t</u>.

Then
$$\frac{dE}{dt} = aCV - kE \quad \ldots\ldots\ldots\ldots\ldots \quad (1)$$

i.e.
$$E = \frac{aCV}{k}(1 - e^{-kt}) \quad \ldots\ldots\ldots\ldots\ldots \quad (2)$$

or, if the dose absorbed in a time <u>t</u> is represented by D,

$$E = \frac{aD}{kt}(1 - e^{-kt}) \quad \ldots\ldots\ldots\ldots\ldots \quad (3)$$

These relations are represented graphically in Figs.4 and 5. In Fig.4 the relative amount of active agent in the tissues (E) is related to the time of exposure (i.e. dose), the inhaled concentration and the respiratory volume being assumed constant. In Fig.5 the total dose is

constant and E is related to the rate of absorption of the dose (i.e. to the concentration inhaled).

It is seen (Fig.4) that at a constant inhaled concentration, E rises with increasing time of exposure, but at a progressively decreasing rate. Fig.5 indicates that for a given dose, E increases at first as the inhaled concentration rises, but then approaches a value which remains almost constant for further increases in concentration. These qualitative results, although based on an elementary conception of the mechanism involved, do not conflict with the present experimental data, and will be examined in further experiments.

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FIG. I. VARIATION IN AIR-WAY RESISTANCE AFTER INHALATION OF G.B. VAPOUR.

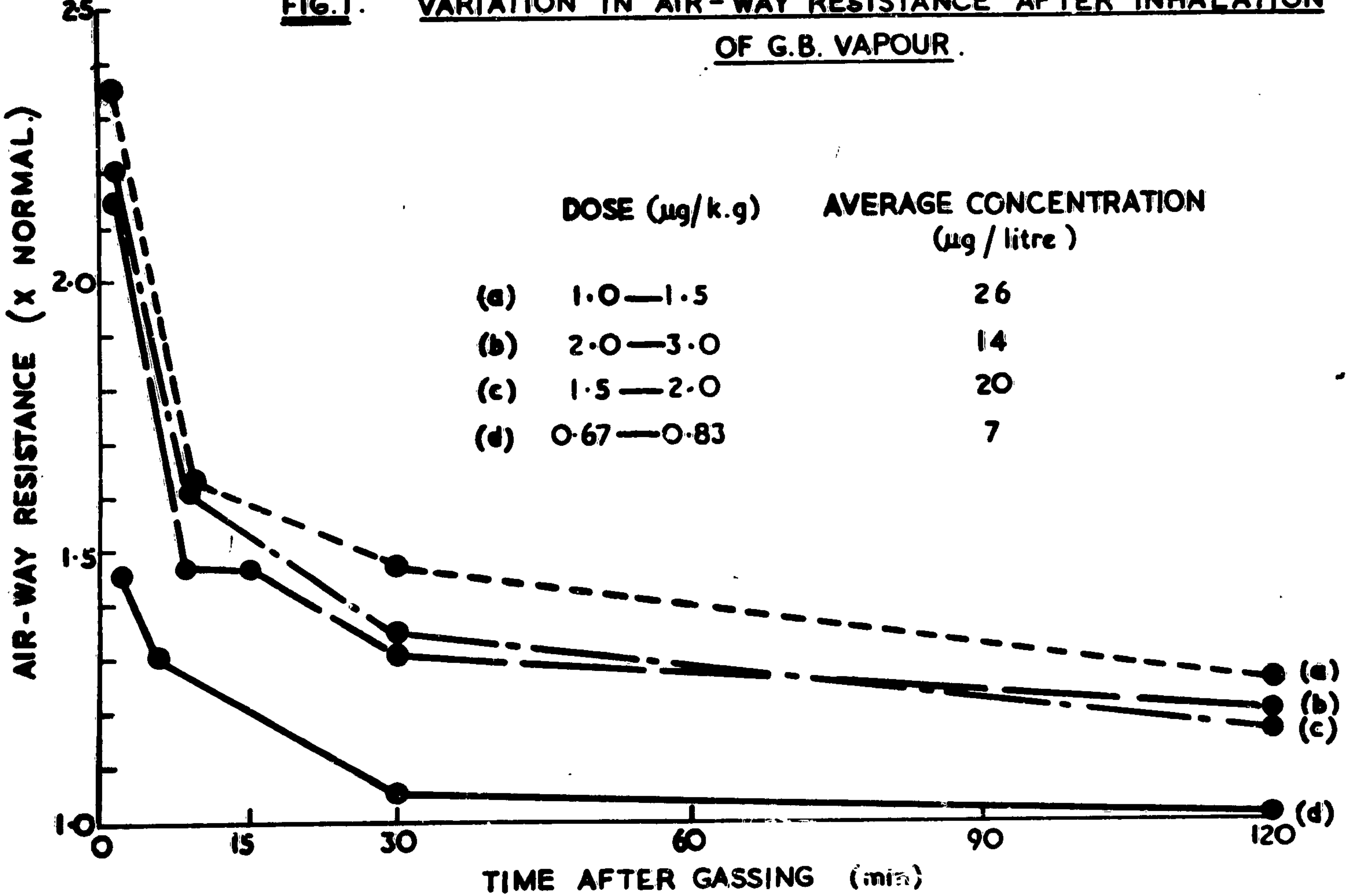
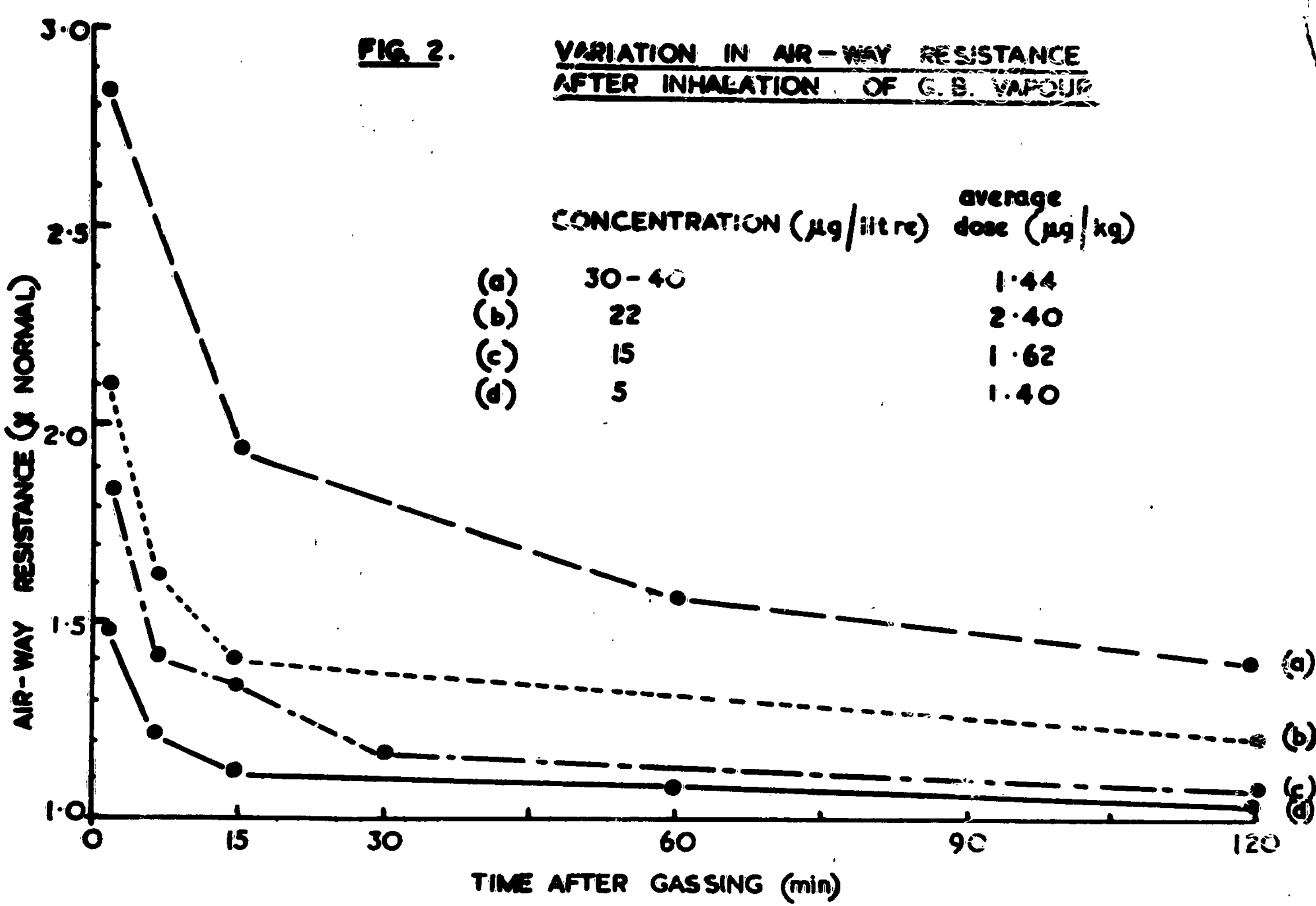


FIG. 2. VARIATION IN AIR-WAY RESISTANCE AFTER INHALATION OF G.B. VAPOUR



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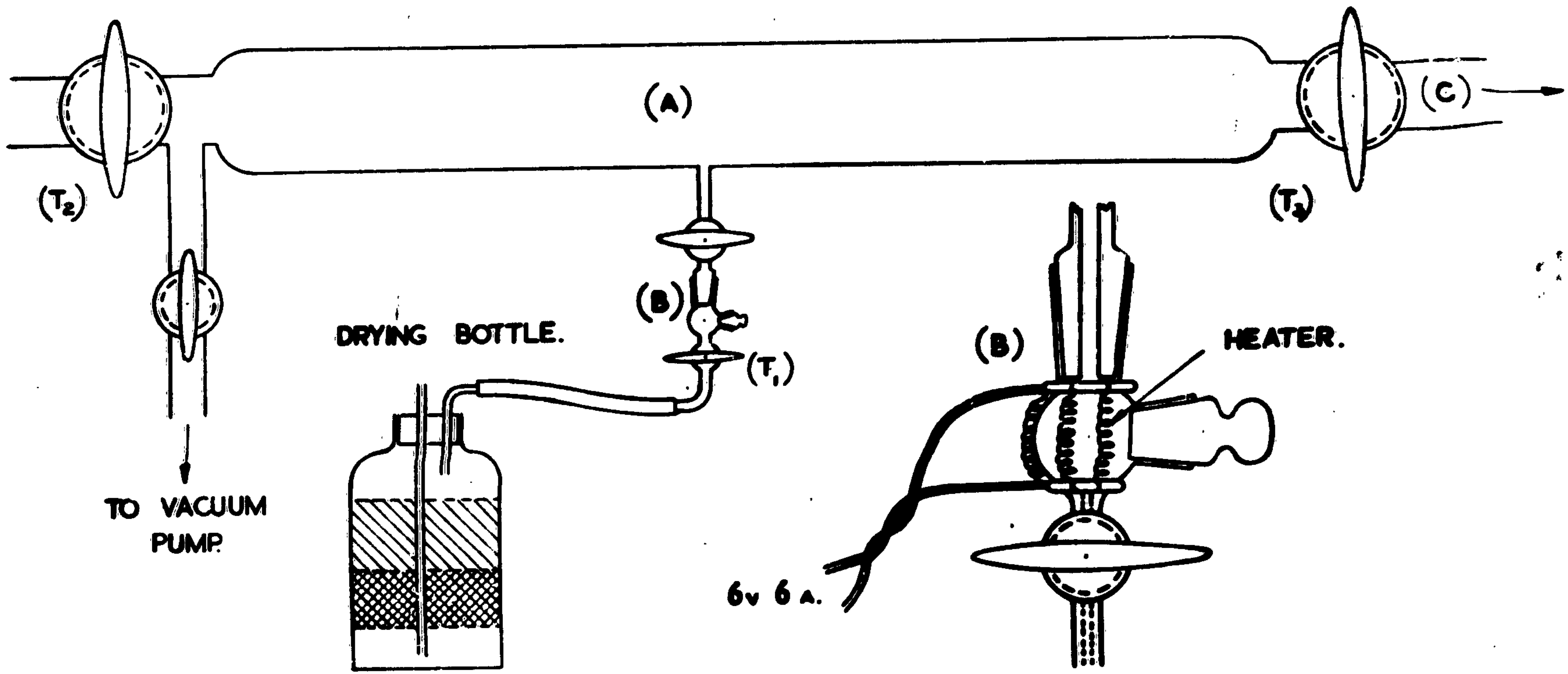

FIG. 3. DEVICE FOR ADMINISTERING KNOWN DOSES OF GB VAPOUR.

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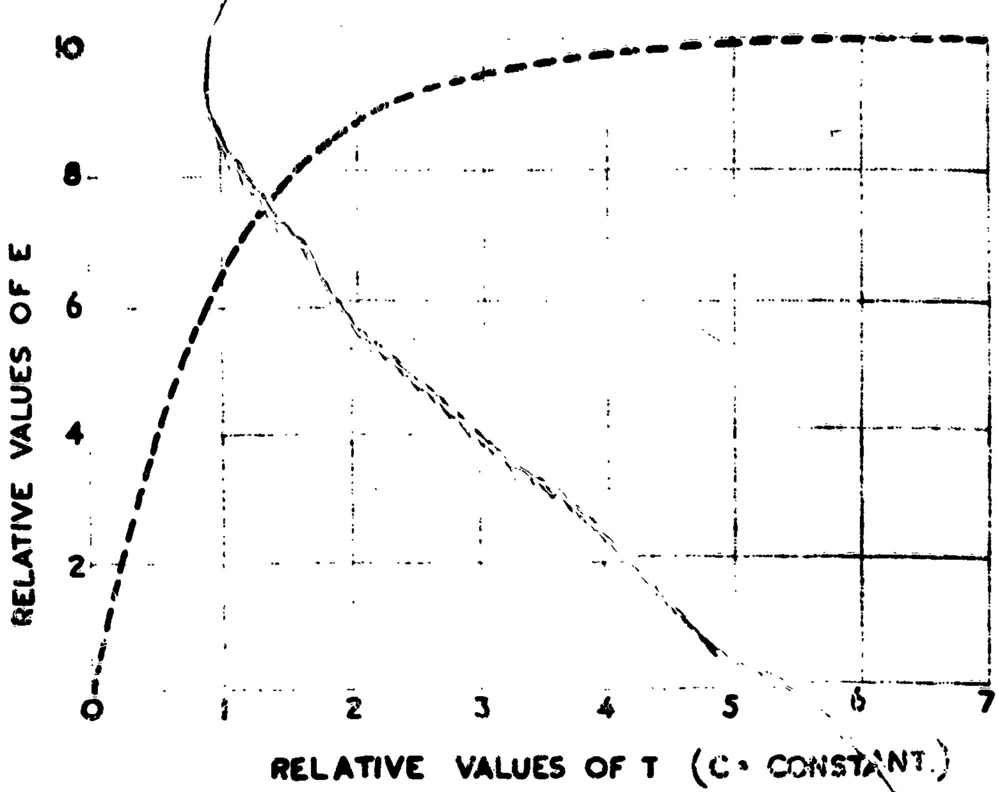

FIG 4.

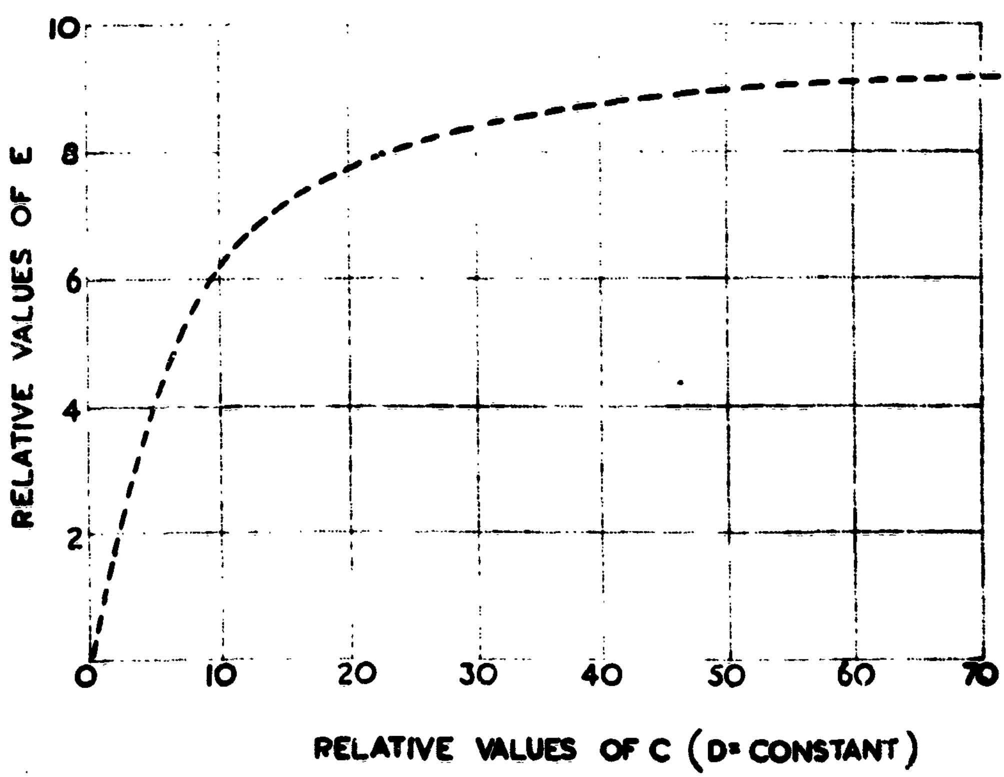

FIG. 5.

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